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Multi-Modality imaging in the assessment of cardiovascular toxicity in the cancer patient

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Abstract

Cancer therapy can be associated with both cardiac and vascular toxicity. Advanced multi-modality imaging can be used to risk stratify patients, identify cardiovascular injury during and after therapy, and prognosticate recovery. Echocardiography continues to be the mainstay in the evaluation of cardiac toxicity. In particular, echocardiography based strain imaging is useful for risk stratification of patients at baseline and detection of sub-clinical LV dysfunction during therapy. Cardiac magnetic resonance (CMR) serves a complementary role in the patient with poor echocardiography or ERNA image quality or in situations where a more accurate and precise LVEF measurement is needed to inform decisions regarding chemotherapy discontinuation. New CMR techniques like T1 and T2 mapping as well as PET imaging will help us better understand the structural, pathological, and metabolic myocardial changes that are associated with ventricular dysfunction or release of serum biomarkers. CMR may also be helpful in the evaluation of the vascular complications of cancer therapy. Stress echocardiography, stress CMR, CT and PET are excellent imaging options in the evaluation of ischemia in patients receiving therapies that could potentially cause vasospasm or accelerated atherosclerosis.

Abbreviations

CAD = coronary artery disease

CMR = cardiac magnetic resonance

CTRCD= chemotherapy-related cardiac dysfunction

EDV= end-diastolic volume

ERNA = equilibrium radionuclide angiocardiology

ESV = end-systolic volume

GLS= global longitudinal strain

GCS= global circumferential strain

GRS= global radial strain

HER2+ = human epidermal growth factor receptor 2 positive

TKIs = tyrosine kinase inhibitors

VEGFi = vascular endothelial growth factor inhibitors

Introduction

The field of oncology has advanced remarkably. In some instances, cancer is either cured or converted into a chronic disease. Nevertheless, some of the old and new emerging cancer therapies are associated with the development of cardiovascular toxicities (1,2), which may have the potential to offset the gains in survival obtained with these cancer breakthroughs.(3) Much of the focus on cardiovascular toxicities has been in the early detection of myocardial damage and the prediction of cancer therapeutics related cardiac dysfunction (CTRCD). However, since the toxicities associated with cancer therapies are much broader (Table # 1)(4), in this manuscript, we review how advanced multi-modality imaging can be used to risk stratify patients before starting cancer therapy, identify early cardiovascular injury during therapy, predict recovery from it, and detect cardiovascular injury in long term cancer survivors.

Clinical case

A 51-year-old female with left sided, high risk, early stage HER2+ breast cancer was referred to the cardio-oncology clinic. Her treatment plan included mastectomy, epirubicin 300mg/m², 17 cycles of trastuzumab, radiation therapy (50Gy), and hormonal therapy. She had no known cardiovascular risk factors, was not receiving medications, and had excellent functional capacity. Imaging and biomarker assessments were performed prior to cancer therapy, throughout her treatment and one year later (Table 2). Her baseline blood pressure was 138/80, cardiac examination was unremarkable, her LVEF by 3D echocardiography was 61%, the global longitudinal strain (GLS) was -21.3%, and the global circumferential strain (GCS) was -20.3%. Several questions were raised during her initial consultation and follow up: How does cardiac imaging play a role in identifying cardiovascular toxicity risk in this patient? What is the best

method to detect early cardiac injury from treatment? What are the predictors of ventricular function recovery after cardiotoxicity?

Assessment of baseline risk of cardiovascular complications in patients receiving cancer therapy

Assessing risk of CTRCD / heart failure

The American Society of Clinical Oncology guidelines recommend risk stratification for cardiac dysfunction prior to initiation of potentially cardio-toxic cancer treatment. We refer the readers to their discussion of which patients with cancer are at increased risk of developing cardiac dysfunction.(5) From the imaging standpoint, patients with borderline cardiac function (left ventricular ejection fraction (LVEF) 50-55%, history of myocardial infarction, and presence of other cardiac comorbidities (e.g. \geq moderate valvular heart disease)) before the start of anthracycline or trastuzumab therapy are at an increased risk (3.6- to 11.8-fold) for developing cardiac dysfunction(5). The expert consensus for the multi-modality imaging evaluation of the adult patient during and after cancer therapy recommends a baseline echocardiogram, with the calculation of LVEF ideally using three dimensional echocardiography and global longitudinal strain (GLS) if the technology is available and the operators are comfortable with their performance and interpretation.(6) The latter is a reflection of the superior reproducibility of 3D LVEF and GLS measurements.(7,8) In addition to LVEF, pre-treatment measurements of GLS appear to identify patients at elevated risk of MACE in the context of anthracycline therapy.(9,10) Similarly every 1% difference in baseline circumferential strain has been associated with a 31% increased odds of cardiotoxicity in women receiving breast cancer therapy.(11)

Cardiac magnetic resonance (CMR) is usually not used as a first-line tool for risk stratification due to its cost and lack of wide availability. However, in patients with a non-diagnostic echocardiogram, unexplained dilation of the left or right ventricles, or morphological abnormalities raising concern for an infiltrative cardiomyopathy, CMR can complement the echocardiographic evaluation to assess for a potential etiology. To date, however, there is no data as to whether pre-treatment CMR parameters identify patients at risk for cardiotoxicity.

Coronary artery disease risk

Stress echocardiography may be useful in the evaluation of patients with intermediate or high probability of CAD, who are undergoing regimens that may be associated with ischemia (e.g 5-fluoracil, bevacizumab, sorafenib and sunitinib).(6) Cardiac computed tomography (CCT) has changed the landscape of coronary assessment in the field of cardiology. Its role in Cardio-oncology is primarily restricted to assessment of coronary calcium and obstructive coronary artery disease.(12). Nuclear and PET stress testing both represent alternatives for the evaluation of CAD in these patients. Stress CMR can detect the presence and extent of inducible myocardial ischemia with high diagnostic accuracy.(13) The attraction of stress echocardiography and stress CMR is the lack of radiation exposure. However, stress echocardiography may be challenging in patients who have had mastectomies, breast expanders or implants. In these situations, the use of ultrasonic enhancing agents may improve visualization of the myocardial segments and accuracy of interpretation.(14) CMR may be not feasible in the presence of certain breast tissue expanders due to their ferromagnetic components.(6)

Vascular toxicity

Many agents used in cancer treatment such as tyrosine kinase inhibitors (TKIs), vascular endothelial growth factor inhibitors (VEGFi) , antimetabolites, and radiation therapy are associated with direct vascular toxicity while hormonal therapy can increase the risk of atherosclerotic vascular events.(15,16) Potential vascular toxicities include, hypertension, coronary artery disease, peripheral arterial disease, pulmonary hypertension, and venous thrombosis.(16) Although certain clinical risk factors for these toxicities have been described (e.g. pre-existing hypertension), unlike cardiomyopathy, there has been no literature examining vascular imaging parameters to identify patients at risk.(16) The area of vascular risk in cancer survivors however has gained significant attention with the description of Clonal Hematopoiesis (CH) as a risk factor for atherosclerotic vascular disease.(17) CH is an expansion of myeloid and lymphoid cells that carry recurrent somatic mutations. CH appears to be identified in approximately 10% of patients aged 70-79(18) with a 4 fold increased incidence in patients receiving cancer therapy compared to untreated patients.(19) Patients with CH are at a 2.0-2.6 fold higher risk of coronary or cerebrovascular disease.(20) Therefore, identifying patients with CH and performing targeted vascular imaging may be a novel future approach to risk stratification.

Early identification of cardiovascular injury during cancer therapy

Early detection of CTRCD

Evaluation of LV volumes and function

Historically, planar equilibrium radionuclide angiography (ERNA) and SPECT-ERNA provided reliable and accurate means of calculation of LVEF. However, although extensive literature exists in the cancer setting, these techniques are almost abandoned due to the concern

of radiation exposure, especially during repeated examinations. In addition, modern multiple gated acquisitions scans (MUGA) may not allow optimal patient positioning for LVEF assessments.(6) The limits of agreement between MUGA and CMR for LVEF are wide (−19.4 to 16.5%). At LVEF threshold of 50%, the cut-off defining cardiac toxicity, there is a risk of misclassification of 35% of cancer patients.(21) It is also important to note the additional limitation of ERNA due to its inability to evaluate right ventricular or valvular function, and pericardial disease.

Although CCT has the capability of providing a measurement of LV volumes and LVEF, it comes at the cost of radiation exposure. Therefore, CCT does not have a routine role in the surveillance of cardiac function or vascular toxicity during cardio-toxic cancer therapy.

Surveillance and detection of CTRCD is currently performed using echo derived LVEF, and more recently strain imaging.(6) The overall goals are: 1) the correct adjudication of Stage B heart failure, so that modern heart failure therapy could be initiated, 2) the accurate calculation of LV volumes in the assessment of LV remodeling; and 3) the potential identification of situations where changes in loading conditions may be playing a role in changes in LVEF or strain.

The best method to measure LVEF to identify early cardiovascular injury is unclear.

CMR can identify small changes in LVEF that appear to parallel the changes in myocardial strain.(22) However, whether such small early changes predict subsequent CTRCD or are just the result of hemodynamic variability is unclear.(23) CMR may be useful clinically in situations where there is concern regarding echocardiographic or equilibrium radionuclide angiography

(ERNA) calculation of LVEF or in situations where a more accurate and precise LVEF measurement is needed to inform decisions regarding chemotherapy discontinuation.(6)

Interestingly recent work in women receiving therapy for breast cancer has suggested that nadir LVEF values are identified by 3D echocardiography earlier than 2D echocardiography suggesting that 3DE measured LVEF may be a useful method to identify early cardiac injury.(24) For adjudication of Stage B heart failure during cancer therapy, based on a single study, 3D LVEF appears to identify more patients who meet CTRCD criteria than 2D LVEF.(25). Accurate calculation of LVEF should be done with the best method available in the echocardiography laboratory (ideally 3D echocardiography).(6) It is important to recognize that although ideal, the technique or the expertise in its interpretation may not be widely available outside academic centers. In such scenarios, ultrasound enhancing agents should be used to enhance 2D echocardiography when two contiguous LV segments are not well visualized on non-contrast apical images.(6)The obtained LV volumes will be larger with closer correlation with CMR. The recently published clinical applications of ultrasonic enhancing agents in echocardiography reported a study examining baseline pre-chemotherapy echocardiograms in female patients where 51% of contrast enhanced diastolic volumes were classified as abnormal, despite the LV dimensions being within the normal range by unenhanced 2D volume measurements. To account for this change in normal range the document proposed an end diastolic volume upper limit cutoff of 83 ml/m² for women and 98 ml/m² for males.(26)

Armstrong et al compared LV volumes measured with 2D and 3D echocardiography against CMR. They found that although the 3D calculated LVEDV and LVESV were closer to the ones calculated by CMR, there was still underestimation (mean EDV 12cc, mean ESV 5cc, p<0.001 for both).(27)

Left ventricular volumes and ejection fraction are not fixed for a given individual. They fluctuate reflecting dynamic changes in loading conditions and inotropic state. A reduction in LVEF can be due to either an increase in LVESV or reduction in LVEDV. In patients treated with anthracycline and/or trastuzumab, the primary driver for a reduction in LVEF is an increase in LVESV.(22,28-30) Patients may exhibit potential reductions in LVEDV caused by intravascular volume depletion (reduced preload) from cancer therapy related poor oral intake, vomiting or diarrhea. Two recent studies of patients with various cancers receiving chemotherapy demonstrated that 16-19% of patients who met criteria for CTRCD only had an isolated reduction in LVEDV without a “significant” increase in LVESV.(23,31) This has important implications for clinical management of sub-clinical LV dysfunction and CTRCD, and is a cause for pause and further investigation. However, several concepts should be considered when interpreting this data. First, up to 6% variability in LVEF and 21ml in LVEDV can occur with CMR measurements due to variability in contouring the basal short axis slice. This is particularly important in longitudinal studies where even the acquisition of the basal slice could be different due to variability in image setup. (32,33) Secondly, based on cardiac physiology, a reduction in LVEDV does not occur in isolation. It is associated with a sympathetic reflex that increases inotropy, which in turn will increase the slope of the end-systolic-pressure volume relationship. In addition the reduction in stroke volume results in reduced systemic pressure with subsequent reduction in afterload. In combination the LVESV also decreases. This concept is supported by recent work where healthy individuals subjected to 2.0-3.5% intravascular volume depletion had a reduction in both LVEDV and LVESV without a statistically significant reduction in LVEF or circumferential strain.(34) Therefore the lack of a reduction in LVESV associated with a

reduction in LVEDV seen in these recent studies suggests a concomitant reduction in myocardial contractility to explain the reduction in LVEF. Finally it is important to recognize without making CMR the technique to routinely follow patients during cancer therapy, that our echocardiography techniques do not have the ability to identify small changes in ventricular volumes during cancer therapy.(8) Hence using ventricular volumes as surrogates of intravascular status would not be practical in routine clinical practice.

The findings of potential volume dependency of LVEF measurements further emphasize the importance of repeating cardiac imaging 2-3 weeks later upon discovery of sub-clinical LV dysfunction or CTRCD before consideration of changes to cancer therapy or initiation of cardiac medications.(6) It is also important to perform the surveillance imaging at times when patients are less likely to be intra-vascular volume depleted, such as the day before the next chemotherapy cycle.

Evaluation of LV deformation: strain imaging.

Negishi et al found that the strongest predictor of CTRCD was delta 2D-based GLS during treatment. An 11% reduction (95% confidence interval, 8.3 to 14.6%) half way through trastuzumab therapy was the optimal cutoff with a sensitivity of 65% and a specificity of 94% for subsequent cardiotoxicity. GLS was an independent early predictor of later reductions in LVEF, incremental to usual predictors in patients at risk for trastuzumab-induced cardiotoxicity. Their findings served as the scaffolding for the subsequently published expert consensus that recommends the use of global longitudinal strain for the surveillance of subclinical LV dysfunction for patients being treated with anthracyclines or trastuzumab with a reduction of >15% compared to baseline illustrating a clinically significant change.(6) Nevertheless, the

association between GLS and subsequent CTRCD may have been potentially misinterpreted postulating that 1) GLS falls before LVEF in patients receiving cardio-toxic therapies and 2) there is a compensatory increase in global circumferential strain (GCS) in response to the reduction in GLS in order to initially preserve LVEF. The recently study published by Stokke et al can help us understand the relationship between LVEF and its determinants: GCS, GLS, LV internal dimension and wall thickness. The model showed that GCS contributes more than twice as much to LVEF when compared with GLS. For the LVEF to be maintained, a reduction of GLS needs to be compensated by an increase in GCS or wall thickness or reduced LV diameter. In the above mentioned study by Negishi et al, LVEF, GLS and GCS decreased in parallel from baseline to 12 months from $58\pm5.5\%$ to $55\pm5.3\%$, from -20.7% to -18.3% , and from -17.8% to -15.9% respectively. GRS decreased from 50.9% to 45.7% .(35) Other studies have also demonstrated simultaneous reduction in all these parameters.(11,36)

The 6-month data from Negishi et al's study can help us understand the limitations of using 2D-echocardiography and the role of 2D based strain for the early detection of sub-clinical LV dysfunction. The LVEF decreased from $64\pm4.6\%$ to $58\pm5.5\%$ (6 absolute point reduction in LVEF), which is below the 10 point threshold ability of 2D based echocardiography to discriminate sequential changes in LVEF.(8) At 12 month follow up, the LVEF continued to deteriorate being reported at $55\pm 5.3\%$ (9 absolute point reduction in LVEF), very close to the threshold giving the reader the ability to recognize the change. In parallel, there was a reduction in GLS from $-20.7\pm2.6\%$ to $-18.3\pm2.1\%$ at 6 months (2.4 absolute reduction, 11.6% relative reduction when compared to baseline), which remained unchanged at 12 months. The lower intra and inter-observer variability of GLS allows easier recognition of the change in systolic function

when compared to LVEF. The relative mean error for GLS is 1.7 (below the 2.4 change noted during surveillance) making 2D based strain well suited for the identification of sub-clinical LV dysfunction.(37)

Using CMR, Drafts et al initially reported on the behavior of LVEF and GCS 1,3 and 6 months in 53 patients receiving low-dose anthracyclines (50-375 mg/m²) for the treatment of breast cancer, leukemia and lymphoma. LVEF and GCS decreased from baseline to 6 months $58 \pm 1\%$ to $53 \pm 1\%$ ($p=0.0002$) and from $-17.7\% \pm 0.4\%$ to -15.1 ± 0.4 , ($p=0.0003$) respectively.(22)

In 101 patients receiving cardio-toxic agents in the setting of various malignancies, Jordan et al subsequently published data incorporating CMR mid-wall eulerian GCS, including this time GLS (n=34, using high-temporal-resolution 2- and 4-chamber cine views), and LVEF.(31)

Overall GLS declined from -15.44 to -14.79 ($p=0.069$), GCS from -17.99 to -17.23% ($p=0.0052$) and LVEF from 59.2 to 56.7% ($p= 0.0002$).

LV mass was unchanged by MRI in the patients who developed CTRCD. The diameter of the ventricle increased only slightly during and after anthracycline therapy.(22)

The data from these echo and CMR studies suggest that the reduction in LVEF may be explained by the parallel reduction in GLS and GCS with slight contribution from the increase in LV internal dimension. The apparent misconception that GLS changes before LVEF appears to be explained by the inability of 2D based echocardiography to recognize changes $<10\%$.

Larger studies ideally using MRI based LVEF and strain are needed to further study this concept.

The significant interest in tri-plane and 3D speckle tracking is currently limited by the poor correlation of values of this technique when compared with 2D based strain. There are two

explanations: the limited feasibility due to poor tracking of the segments and the differences in acquisition rates (low volumes per second when compared to the high frame rates attainable with its 2D counterpart). We are hopeful that technology will evolve over time overcoming these challenges.(38)

Tissue characterization

CMR may facilitate our understanding of the pathogenesis of CTRCD. Myocardial tissue changes such as intracellular and interstitial edema and fibrosis may precede the alterations in LV volumes, reduction in LVEF, or changes in myocardial strain and may represent early markers of myocardial injury. Multiple CMR imaging sequences such as T1 and T2 weighted imaging, as well as newer T2 and T1 mapping sequences can help identify intracellular and interstitial edema and are now part of our armamentarium (Figure 1).(39,40) Native T1 mapping or a combination of pre and post contrast T1 mapping can be used to calculate extracellular volume fraction (ECV) as a marker of edema or interstitial fibrosis.(41) Post-contrast T1 weighted imaging (late gadolinium enhancement, LGE) can be used to identify myocardial replacement fibrosis

Several small studies using CMR have shown myocardial edema early following anthracycline therapy using T2 weighted sequences.(30,42)The presence of edema has been associated with persistent reduction in RV function in follow-up. (30) CMR studies have also demonstrated presence of focal and replacement fibrosis with variable patterns (epicardial, mid-wall, insertion points) and incidence. Nevertheless this finding has not been consistent in the literature.(40) Also, there is accumulating evidence of the presence of diffuse interstitial fibrosis measured by

native T1 mapping and ECV in anthracycline-induced cardiomyopathy. It manifests independent of the presence of cardiovascular comorbidities and is associated with impaired diastolic function.(43,44) In cancer survivors, an increase in ECV has been associated with higher anthracycline doses and lower exercise capacity.(45) In this latter cohort the increase in ECV is likely a marker of interstitial fibrosis.

Some CMR studies have described subepicardial LGE of the lateral wall in patients with trastuzumab cardiomyopathy, suggesting an underlying myocarditis, however, this has not been reproduced in other studies. (46,47) Whilst the presence of LGE has been associated with prognosis in a range of ischemic and non-ischemic cardiomyopathies, there is no similar data in patients with CTRCD.(48) However, LGE imaging may have value in evaluation of patients receiving cancer immunotherapy with a clinical suspicion for myocarditis. Cardiotoxicity related to immunotherapy includes heart failure, Takotsubo-Like syndrome and fulminant myocarditis with fatal outcome(49). CMR is known to be a valuable modality for detection of myocarditis using the Lake Louise Criteria.(50) Although this has not been formally evaluated in the setting of immune therapy, a recent case series of 35 patients with immune therapy mediated myocarditis identified LGE in a mid-myocardial, sub-epicardial or diffuse pattern in 77% of the patients (Figure 2).(51)

Myocardial metabolism

PET imaging provides a unique assessment of myocardial metabolism, which may identify the earliest myocardial or vascular changes related to toxicity. Although changes in FDG uptake

appear to identify patients at risk of doxorubicin mediated cardiotoxicity (52), the use of PET imaging to identify early cardio-toxicity is still limited to the research realm.

Complementary role of biomarkers.

Several biomarkers have been proposed for early detection of CTRCD, the most studied ones are troponin, resulting from cardiomyocyte damage and natriuretic peptides reflecting elevation in left ventricular filling pressure and wall stress. Troponin is recognized as a highly efficient predictor of early and long-term cardiac toxicity. Cardinale et al had previously demonstrated that Tn I positivity, soon after anthracycline containing regimens is a strong predictor of LVEF reduction and poor cardiac outcome, particularly in patients showing persistent (> 1 month) troponin positivity.(53-55) Her group also showed that in trastuzumab treated patients, TNI evaluation provides an opportunity to recognize patients at risk of developing trastuzumab induced CTRCD and among them, those who are less likely to recover from it despite optimal heart failure therapy.(56) There is debate regarding the clinical usefulness of the measurement of natriuretic peptides because of discordant results (1,2). Noteworthy, data on the complementary role of biomarkers to imaging in cancer patients are yet limited but encouraging. Sawaya et al. showed a negative predictive value of 91% when a decrease in GLS (<19%) was combined with an elevation of ultrasensitive TnI in breast cancer patients receiving doxorubicin and trastuzumab.(57) Similarly, the combination of elevated TnI and MPO levels was shown to identify a group of patients with breast cancer at increased risk for cardiotoxicity than each individual biomarker alone.(58) A combined multimodality imaging / biomarker approach in selected individuals may thus be of interest for risk prediction and to guide therapy.

Detection of pulmonary hypertension

Pulmonary hypertension can occur during cancer treatment due to venous thromboembolism, compression by the tumor, or due to use of tyrosine kinase inhibitors such as dasatinib.

Echocardiography remains the primary method to screen for pulmonary hypertension during treatment via the measurement of right ventricular systolic pressure from the tricuspid regurgitation jet.

Vascular toxicity

There has been growing interest in expanding our understanding of the effects of cancer therapeutics in the cardiovascular system beyond the heart. Arterial stiffness by pulse wave velocity (PWV) can identify vascular changes in the asymptomatic sub-clinical stage: vascular ultrasound can assess both the local and carotid-femoral arterial stiffness, whilst MRI can assess both the local and the central arterial stiffness. Di et al have recently reviewed cancer therapy therapy-induced vascular toxicity.(59) Useful imaging biomarkers in this context are the non-invasive flow-mediated dilation (flow hyperemic mediated dilation) of the brachial artery to detect endothelial dysfunction and increased intima-media thickness of the common carotid artery measured by ultrasound. Using CMR, thoracic aortic pulse wave velocity (PWV), a marker of vascular stiffness, appears to increase steadily after the administration of anthracyclines. While adjusting for baseline heart rate had minimal impact on the change in velocity over time, participants with a higher systolic blood pressure had a higher pulse wave velocity at rest and a faster increase in PWV, highlighting the interaction between the effects of the chemotherapeutic agents and the baseline risk factors of the patient. Aortic distensibility can also be assessed by gated computed tomography but both the radiation burden and lower

temporal resolution (which may lead to underestimation of distensibility) limit its use in this context .(60) Despite these interesting findings, whether these early changes result in subsequent symptomatic vascular disease remains unknown.

Prediction of recovery of cardiovascular toxicity

CTRCD

Once there is a reduction in myocardial function identified during cancer therapy, there is very little data on predictors of recovery other than the timing of heart failure therapy initiation.(61) In patients receiving sequential anthracycline and trastuzumab based therapy nadir GLS value greater than -15.8% may identify patients at higher risk of lack of LVEF recovery (HR 0.39, 95% CI 0.18-0.74).(62) Similarly in anthracycline treated patients, lower LVEF at initiation of HF treatment may be associated with lack of recovery of ventricular function.(63) The only other imaging predictors of ventricular function recovery is larger left atrial volume (OR 0.94, 95% CI 0.88-0.99).(64) These parameters together suggest that those who have more severe myocardial dysfunction as measured by EF, strain, or atrial remodeling at initiation of HF therapy are less likely to have recovery of heart function.

Detection of cardiovascular disease in long-term cancer survivors

Detection of CTRCD

The high risk for adult onset CTRCD after treatment for childhood and adolescent neoplasia warrants early detection when intervention is expected to be of greater benefit. The Children's Oncology group long-term follow up guidelines recommend periodic evaluation by echocardiography. Traditionally, the measurement has been obtained using two-dimensional

echocardiography. In cancer survivors, compared with CMR, the sensitivity and false-negative rate improve from 25% and 75% to 53% and 47% respectively when using 3D echocardiography instead of 2D echocardiography, reducing the misclassification rate of Stage B heart failure patients as normal from 11% to 5%.(27) However, in a larger cohort of 1820 adult survivors of childhood cancer, while only 5.8% of the patients had abnormal 3D LVEFs ($< 50\%$), 32.1% of survivors with normal 3D LVEF had cardiac dysfunction by GLS (28%), by diastolic assessment (8.7%), or both. Abnormal GLS was associated with the dose of chest radiation and anthracyclines based chemotherapy received. Interestingly, survivors with the metabolic syndrome were twice as likely to have abnormal GLS or diastolic dysfunction. They concluded that the use of modern echocardiography may allow identification of a subset of survivors who may benefit from early medical intervention.(65)

CMR based extracellular volume fraction (ECV) has been examined as a measure of subclinical cardiac injury in both pediatric and adult cancer survivors. In pediatric cancer survivors ECV appears to be associated with total anthracycline dose, markers of adverse ventricular remodeling, and lower VO₂ max.(45) In anthracycline treated adults ECV fraction is increased in cancer survivors compared to controls, with higher values in those with reduced versus preserved LVEF(44) Elevated ECV is also correlated with measures of worse diastolic dysfunction such as higher lateral annular E' velocity and E/e' ratio. Compared to matched controls and a separate cohort of patients imaged prior to cancer therapy, ECV values appear to be elevated particularly in those receiving anthracycline based therapy.(43) These data suggest that increased ECV may occur in cancer survivors with preserved or reduced LVEF and that it identifies a cohort of patients with potentially vulnerable myocardium. Whether these

abnormalities have future implications for the cardiovascular health of patients remains to be determined.

In addition to LV dysfunction recent studies of lymphoma survivors have also described right ventricular (RV) systolic dysfunction. The association between LV function (LV global longitudinal strain) and RV function (tricuspid annular plane systolic excursion), indicated a global long-term cardiotoxic effect. However, RV dysfunction (6.2%) was less prevalent than LV dysfunction (30.8%) ($p < 0.001$).^(66,67)

Detection of pericardial disease

Pericardial disease can be seen as a long term consequence of radiation therapy to the chest. Echocardiography remains the primary modality to screen for pericardial constriction in patients with suggestive symptoms.⁽⁶⁸⁾ Cardiac CT can help assess the presence and extent of pericardial calcification (Figure 3). In patients in whom echocardiography is not diagnostic, cardiac MRI also provides an assessment of the presence of pericardial thickening, its extent, as well an assessment of the constrictive physiology (Figure 3).⁽⁶⁸⁾

Detection of vascular toxicity

Radiation-induced cardiovascular disease appears to be associated with damage to endothelial cells via transient increases in oxidative stress, impaired vascular wall homeostasis, endothelial dysfunction and apoptosis of endothelial cells, subsequent inflammatory response leading to increased expression of matrix metalloproteinases, adhesion molecules, and proinflammatory cytokines and downregulation of vasculoprotective nitric oxide, leading to accelerated

atherosclerosis, increased blood viscosity and unstable platelet aggregates(69). Arterial stiffness is a precursor of atherosclerosis and is increased in irradiated arteries, in keeping with radiation-induced damage. Early and late changes in markers of aortic stiffness with breast cancer therapy was measured with CMR at baseline, 1, 4 and 14 months post-therapy measuring aortic pulse wave velocity (PWV) and distensibility at ascending aorta and proximal descending aorta. They demonstrated that acute changes are observed in PWV and distensibility at the ascending aorta following contemporary breast cancer chemotherapy and partially reverse a year after therapy is discontinued, with more severe effects seen with anthracyclines.(70) Childhood cancer survivors show a reduced vascular health(71) and increase in arterial stiffness was also demonstrated in following chemotherapy.(72) The long-term effects of radiotherapy on arterial stiffness can be involved in increasing cardiovascular risk in breast cancer-treated women.(73)

The assessment of coronary calcium and obstructive coronary artery disease can be achieved robustly using cardiac computed tomography (CCT)(Figure 4) and stress CMR (Figure #5). In survivors, a coronary calcium score may help with risk stratification and guide intensity of risk factor modification.

Discussion about the patient

Our patient had no traditional cardiovascular risk factors. Although her baseline 3D LVEF and GLS were normal, her GCS was mildly reduced which may be a pre-treatment risk of CTRCD (Table 2).(11) She has a reduction in 3D LVEF immediately post anthracycline but not meeting CTRCD criteria. However, she had >15% relative reduction in GLS meeting criteria for subclinical LV dysfunction.(6) Given the absence of convincing data for intervention with isolated reduction in GLS, no cardiac therapy was instituted. She presented 1 month later with

stage C HF. Her lowest GLS was measured at 15.1% suggesting that there is a reduced chance of completed LVEF recovery. (62) With 2 trastuzumab cycles held and initiation of beta-blockers and ACE inhibitors, her LVEF and GLS improved, however, despite ~2 years of cardiac medications her GLS and LVEF remains mildly reduced.

Outcomes in Cardio-Oncology and Future directions.

The goal for the cancer patient is to fully administer the prescribed regimen with no interruptions, aiming at cure or remission, with a survival free of cardiovascular morbidity and mortality. This brings us to the question as to the optimal outcome to follow in Cardio-oncology?

We propose to strengthen the partnership between imaging, oncology and heart failure specialists and very importantly, the cancer patient so as a group we can come to an agreement as to the outcomes we believe will matter, so we can use them effectively to understand and mitigate the cardiovascular toxicity of old and new agents. We anticipate that the oncologists will include the ability to deliver full and uninterrupted regimens. We the imagers, would like to include LV volumes, LVEF and mass and deformation indices. Our heart failure colleagues will obviously be interested in the accurate adjudication of cardiomyopathy, heart failure and cardiovascular mortality as well as the use of biomarkers (troponin, BNP and NT-BNP) and tests evaluating functional exercise capacity (6 minute walk test and VO₂ max). The patient would likely add quality of life to the above-mentioned metrics.

Regardless of our field of expertise, we have one shared goal: cancer survival without cardiovascular disease. We look forward to continuing the advancement of the field of

multimodality imaging with the hope achieving this goal through the demonstration of impact on outcomes.

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Disclosures

CBD is a consultant for Circle Cardiovascular Imaging (Calgary, Canada).

References

1. Moslehi JJ. Cardiovascular Toxic Effects of Targeted Cancer Therapies. *N Engl J Med* 2016;375:1457-1467.
2. Yeh ET, Chang HM. Oncocardiology-Past, Present, and Future: A Review. *JAMA cardiology* 2016.
3. Abdel-Qadir H, Austin PC, Lee DS et al. A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer. *JAMA cardiology* 2017;2:88-93.
4. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009;53:2231-47.
5. Armenian SH, Lacchetti C, Barac A et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2017;35:893-911.
6. Plana JC, Galderisi M, Barac A et al. Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2014;27:911-39.
7. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *European heart journal cardiovascular Imaging* 2015;16:233-70.
8. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popovic ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. *J Am Coll Cardiol* 2013;61:77-84.
9. Ali MT, Yucel E, Bouras S et al. Myocardial Strain Is Associated with Adverse Clinical Cardiac Events in Patients Treated with Anthracyclines. *J Am Soc Echocardiogr* 2016;29:522-527 e3.
10. Mousavi N, Tan TC, Ali M, Halpern EF, Wang L, Scherrer-Crosbie M. Echocardiographic parameters of left ventricular size and function as predictors of symptomatic heart failure in patients with a left ventricular ejection fraction of 50-59% treated with anthracyclines. *European heart journal cardiovascular Imaging* 2015.
11. Narayan HK, French B, Khan AM et al. Noninvasive Measures of Ventricular-Arterial Coupling and Circumferential Strain Predict Cancer Therapeutics-Related Cardiac Dysfunction. *JACC Cardiovasc Imaging* 2016;9:1131-1141.
12. Lancellotti P, Nkomo VT, Badano LP et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr* 2013;26:1013-32.
13. Authors/Task Force m, Windecker S, Kolh P et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of

- Percutaneous Cardiovascular Interventions (EAPCI). *European heart journal* 2014;35:2541-619.
14. Plana JC, Mikati IA, Dokainish H et al. A randomized cross-over study for evaluation of the effect of image optimization with contrast on the diagnostic accuracy of dobutamine echocardiography in coronary artery disease The OPTIMIZE Trial. *JACC Cardiovasc Imaging* 2008;1:145-52.
 15. Goldvaser H, Barnes TA, Seruga B et al. Toxicity of Extended Adjuvant Therapy With Aromatase Inhibitors in Early Breast Cancer: A Systematic Review and Meta-analysis. *Journal of the National Cancer Institute* 2018;110.
 16. Herrmann J, Yang EH, Iliescu CA et al. Vascular Toxicities of Cancer Therapies: The Old and the New--An Evolving Avenue. *Circulation* 2016;133:1272-89.
 17. Jaiswal S, Natarajan P, Silver AJ et al. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. *N Engl J Med* 2017;377:111-121.
 18. Genovese G, Kahler AK, Handsaker RE et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med* 2014;371:2477-87.
 19. Coombs CC, Zehir A, Devlin SM et al. Therapy-Related Clonal Hematopoiesis in Patients with Non-hematologic Cancers Is Common and Associated with Adverse Clinical Outcomes. *Cell stem cell* 2017;21:374-382 e4.
 20. Jaiswal S, Fontanillas P, Flannick J et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med* 2014;371:2488-98.
 21. Huang H, Nijjar PS, Misialek JR et al. Accuracy of left ventricular ejection fraction by contemporary multiple gated acquisition scanning in patients with cancer: comparison with cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2017;19:34.
 22. Drafts BC, Twomley KM, D'Agostino R, Jr. et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. *JACC Cardiovasc Imaging* 2013;6:877-85.
 23. Melendez GC, Sukpraphrute B, D'Agostino RB, Jr. et al. Frequency of Left Ventricular End-Diastolic Volume-Mediated Declines in Ejection Fraction in Patients Receiving Potentially Cardiotoxic Cancer Treatment. *Am J Cardiol* 2017;119:1637-1642.
 24. Zhang KW, Finkelman BS, Gulati G et al. Abnormalities in 3-Dimensional Left Ventricular Mechanics With Anthracycline Chemotherapy Are Associated With Systolic and Diastolic Dysfunction. *JACC Cardiovasc Imaging* 2018.
 25. Santoro C, Arpino G, Esposito R et al. 2D and 3D strain for detection of subclinical anthracycline cardiotoxicity in breast cancer patients: a balance with feasibility. *European heart journal cardiovascular Imaging* 2017;18:930-936.
 26. Porter TR, Mulvagh SL, Abdelmoneim SS et al. Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update. *J Am Soc Echocardiogr* 2018;31:241-274.
 27. Armstrong GT, Plana JC, Zhang N et al. Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic resonance imaging. *J Clin Oncol* 2012;30:2876-84.
 28. Pituskin E, Mackey JR, Koshman S et al. Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101-Breast): A Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity. *J Clin Oncol* 2017;35:870-877.

29. Jordan JH, D'Agostino RB, Jr., Hamilton CA et al. Longitudinal assessment of concurrent changes in left ventricular ejection fraction and left ventricular myocardial tissue characteristics after administration of cardiotoxic chemotherapies using T1-weighted and T2-weighted cardiovascular magnetic resonance. *Circ Cardiovasc Imaging* 2014;7:872-9.
30. Grover S, Leong DP, Chakrabarty A et al. Left and right ventricular effects of anthracycline and trastuzumab chemotherapy: A prospective study using novel cardiac imaging and biochemical markers. *International journal of cardiology* 2013;168:5465-7.
31. Jordan JH, Sukpraphrute B, Melendez GC, Jolly MP, D'Agostino RB, Jr., Hundley WG. Early Myocardial Strain Changes During Potentially Cardiotoxic Chemotherapy May Occur as a Result of Reductions in Left Ventricular End-Diastolic Volume: The Need to Interpret Left Ventricular Strain With Volumes. *Circulation* 2017;135:2575-2577.
32. Marchesseau S, Ho JX, Totman JJ. Influence of the short-axis cine acquisition protocol on the cardiac function evaluation: A reproducibility study. *European journal of radiology open* 2016;3:60-6.
33. Marcus JT, Gotte MJ, DeWaal LK et al. The influence of through-plane motion on left ventricular volumes measured by magnetic resonance imaging: implications for image acquisition and analysis. *J Cardiovasc Magn Reson* 1999;1:1-6.
34. Stohr EJ, Gonzalez-Alonso J, Pearson J et al. Dehydration reduces left ventricular filling at rest and during exercise independent of twist mechanics. *Journal of applied physiology* 2011;111:891-7.
35. Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. *J Am Soc Echocardiogr* 2013;26:493-8.
36. Narayan HK, Finkelman B, French B et al. Detailed Echocardiographic Phenotyping in Breast Cancer Patients: Associations With Ejection Fraction Decline, Recovery, and Heart Failure Symptoms Over 3 Years of Follow-Up. *Circulation* 2017;135:1397-1412.
37. Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP, Voigt JU. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. *J Am Soc Echocardiogr* 2015;28:1171-1181, e2.
38. Negishi K, Negishi T, Agler DA, Plana JC, Marwick TH. Role of temporal resolution in selection of the appropriate strain technique for evaluation of subclinical myocardial dysfunction. *Echocardiography* 2012;29:334-9.
39. Ferreira VM, Piechnik SK, Dall'Armellina E et al. Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2012;14:42.
40. Thavendiranathan P, Wintersperger BJ, Flamm SD, Marwick TH. Cardiac MRI in the assessment of cardiac injury and toxicity from cancer chemotherapy: a systematic review. *Circ Cardiovasc Imaging* 2013;6:1080-91.
41. Kellman P, Wilson JR, Xue H et al. Extracellular volume fraction mapping in the myocardium, part 2: initial clinical experience. *J Cardiovasc Magn Reson* 2012;14:64.

42. Oberholzer K, Kunz RP, Dittrich M, Thelen M. [Anthracycline-induced cardiotoxicity: cardiac MRI after treatment for childhood cancer]. *RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin* 2004;176:1245-50.
43. Jordan JH, Vasu S, Morgan TM et al. Anthracycline-Associated T1 Mapping Characteristics Are Elevated Independent of the Presence of Cardiovascular Comorbidities in Cancer Survivors. *Circ Cardiovasc Imaging* 2016;9.
44. Neilan TG, Coelho-Filho OR, Shah RV et al. Myocardial extracellular volume by cardiac magnetic resonance imaging in patients treated with anthracycline-based chemotherapy. *Am J Cardiol* 2013;111:717-22.
45. Tham EB, Haykowsky MJ, Chow K et al. Diffuse myocardial fibrosis by T1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling. *J Cardiovasc Magn Reson* 2013;15:48.
46. Wadhwa D, Fallah-Rad N, Grenier D et al. Trastuzumab mediated cardiotoxicity in the setting of adjuvant chemotherapy for breast cancer: a retrospective study. *Breast cancer research and treatment* 2009;117:357-64.
47. Fallah-Rad N, Lytwyn M, Fang T, Kirkpatrick I, Jassal DS. Delayed contrast enhancement cardiac magnetic resonance imaging in trastuzumab induced cardiomyopathy. *J Cardiovasc Magn Reson* 2008;10:5.
48. Bucciarelli-Ducci C, Azevedo CF. On fibrosis, prognosis, and the unique role of CMR: a paradigm shift from "bright is dead" to "bright is bad". *J Am Coll Cardiol* 2014;64:155-7.
49. Asnani A. Cardiotoxicity of Immunotherapy: Incidence, Diagnosis, and Management. *Current oncology reports* 2018;20:44.
50. Friedrich MG, Sechtem U, Schulz-Menger J et al. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. *J Am Coll Cardiol* 2009;53:1475-87.
51. Mahmood SS, Fradley MG, Cohen JV et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. *J Am Coll Cardiol* 2018;71:1755-1764.
52. Bauckneht M, Ferrarazzo G, Fiz F et al. Doxorubicin Effect on Myocardial Metabolism as a Prerequisite for Subsequent Development of Cardiac Toxicity: A Translational (18)F-FDG PET/CT Observation. *J Nucl Med* 2017;58:1638-1645.
53. Cardinale D, Sandri MT, Colombo A et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation* 2004;109:2749-54.
54. Cardinale D, Sandri MT, Martinoni A et al. Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. *Ann Oncol* 2002;13:710-5.
55. Cardinale D, Sandri MT, Martinoni A et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol* 2000;36:517-22.
56. Cardinale D, Colombo A, Torrisi R et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. *J Clin Oncol* 2010;28:3910-6.
57. Sawaya H, Sebag IA, Plana JC et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circ Cardiovasc Imaging* 2012;5:596-603.

58. Ky B, Putt M, Sawaya H et al. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. *J Am Coll Cardiol* 2014;63:809-16.
59. Di Lisi D, Madonna R, Zito C et al. Anticancer therapy-induced vascular toxicity: VEGF inhibition and beyond. *International journal of cardiology* 2017;227:11-17.
60. Ganten M, Boese JM, Leitermann D, Semmler W. Quantification of aortic elasticity: development and experimental validation of a method using computed tomography. *European radiology* 2005;15:2506-12.
61. Cardinale D, Colombo A, Lamantia G et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol* 2010;55:213-20.
62. Fei HW, Ali MT, Tan TC et al. Left Ventricular Global Longitudinal Strain in HER-2 + Breast Cancer Patients Treated with Anthracyclines and Trastuzumab Who Develop Cardiotoxicity Is Associated with Subsequent Recovery of Left Ventricular Ejection Fraction. *Echocardiography* 2016;33:519-26.
63. Cardinale D, Colombo A, Bacchiani G et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation* 2015;131:1981-8.
64. Oliveira GH, Mukerji S, Hernandez AV et al. Incidence, predictors, and impact on survival of left ventricular systolic dysfunction and recovery in advanced cancer patients. *Am J Cardiol* 2014;113:1893-8.
65. Armstrong GT, Joshi VM, Ness KK et al. Comprehensive Echocardiographic Detection of Treatment-Related Cardiac Dysfunction in Adult Survivors of Childhood Cancer: Results From the St. Jude Lifetime Cohort Study. *J Am Coll Cardiol* 2015;65:2511-22.
66. Murbraech K, Holte E, Broch K et al. Impaired Right Ventricular Function in Long-Term Lymphoma Survivors. *J Am Soc Echocardiogr* 2016;29:528-36.
67. Chang WT, Shih JY, Feng YH et al. The Early Predictive Value of Right Ventricular Strain in Epirubicin-Induced Cardiotoxicity in Patients with Breast Cancer. *Acta Cardiologica Sinica* 2016;32:550-559.
68. Verhaert D, Gabriel RS, Johnston D, Lytle BW, Desai MY, Klein AL. The role of multimodality imaging in the management of pericardial disease. *Circ Cardiovasc Imaging* 2010;3:333-43.
69. Tribble DL, Barcellos-Hoff MH, Chu BM, Gong EL. Ionizing radiation accelerates aortic lesion formation in fat-fed mice via SOD-inhibitable processes. *Arteriosclerosis, thrombosis, and vascular biology* 1999;19:1387-92.
70. Grover S, Lou PW, Bradbrook C et al. Early and late changes in markers of aortic stiffness with breast cancer therapy. *Internal medicine journal* 2015;45:140-7.
71. Ruble K, Davis CL, Han HR. Endothelial health in childhood acute lymphoid leukemia survivors: pilot evaluation with peripheral artery tonometry. *J Pediatr Hematol Oncol* 2015;37:117-20.
72. Krystal JI, Reppucci M, Mayr T, Fish JD, Sethna C. Arterial stiffness in childhood cancer survivors. *Pediatric blood & cancer* 2015;62:1832-7.
73. Vallerio P, Sarno L, Stucchi M et al. Long-Term Effects of Radiotherapy on Arterial Stiffness in Breast Cancer Women. *Am J Cardiol* 2016;118:771-6.

Figure Legends

Figure 1: CMR tools to understand the underlying mechanisms of cardiotoxicity. (Panels A and B) Cardiac MRI studies in a patient during and after 6-month withdrawal of trastuzumab: end-diastolic (EDV) frame, end-systolic (ESV) frame, feature tracking analysis and curves and native T1 mapping. At 6-month withdrawal, both EDV and ESV are reduced, ejection fraction increased, longitudinal strain improved, and native T1 values were reduced. This case demonstrated the reversible nature of trastuzumab cardiomyopathy. (Panel C) CMR study in a patient with anthracycline-cardiomyopathy, with reduced EDV and ESV, reduced ejection, impaired global longitudinal strain, and presence of subepicardial and mid-wall late gadolinium enhancement (LGE) in the septum, inferior and inferolateral walls.

Figure 2: Myocarditis identified by cardiac MRI. Panel A demonstrates a focal area of myocardial edema on spectral attenuated inversion recovery (SPAIR) image (arrow) while panel B demonstrated sub-epicardial enhancement (arrow) on late gadolinium enhancement images reflective of myocardial cell death. The sub-epicardial enhancement is a pattern often seen in myocarditis.

Figure 3: Assessment of pericardial constriction using cardiac MRI. Panel A demonstrates a T1 weighted spin echo sequence demonstrating thickening of the pericardium (arrow). Panel B and C demonstrate a real time cine sequence with normal position of the interventricular septum in expiration (Panel B), but shift into the LV during inspiration (Panel C). This finding of respirophasic septal shift is a hemodynamic feature of constrictive physiology.

Figure 4: Cardiac computed tomography for assessment of coronary artery disease. In patients with prior chest radiation Panel A demonstrates pericardial calcification, panel B significant proximal coronary artery disease involving the left anterior descending. Panel C demonstrates mixed plaque in proximal LAD in a patient experience chest pain during treatment with 5-fluorauracil.

Figure 5: Significant peri-infarct ischemia (panel A, white arrow) in the basal to mid-cavity of the anterior wall (LAD territory) in a 57 year old male with a prior history of chemotherapy and radiation for small cell lung cancer.

Panel A: Basal, mid, apical short-axis slice first pass perfusion images using a GRE sequence after adenosine infusion and administration of 0.1 mmol/kg of gadolinium chelate contrast agent.

Panel B: corresponding basal, mid, apical short-axis late gadolinium enhancement images using a IR-GRE sequence 15-20min after contrast administration.

Table 1: Cardiovascular toxicities where Imaging plays a role in risk stratification, detection or prognosis

Toxicity	Agents	Imaging recommended
CTRCD / Myocarditis	Anthracyclines Alkylating agents Antimetabolites Antimicrotubule agents Monoclonal antibody based tyrosine kinase inhibitors Proteasome inhibitors Small molecule tyrosine kinase inhibitors Immune therapy	3D Echo (ideally) / 2D Echo GLS CMR
Valvular heart disease	Radiation induced heart disease	2D Echo CMR
Pericardial disease	Methotrexate Arsenic trioxide Antimetabolites Abtimicrotubule agents Radiation therapy	2D Echo CT CMR
Coronary artery disease	Antimetabolites Antimicrotubule agents Monoclonal antibody based	Stress echocardiography CCT Stress CMR

	tyrosine-kinase inhibitors Small molecule tyrosine kinase inhibitors	PET
Pulmonary hypertension	Small molecule tyrosine kinase inhibitors	2D Echo
Vascular toxicity	Anthracyclines	Vascular ultrasound CMR

Table 2: Temporal changes in cardiac function, biomarkers, and symptoms in the clinical case presented.

Time	3D EF	2D EF	GLS	HsTpI	NYHA
Pre cancer therapy	61	64	-21.5	2	I
Post anthracycline	53	55	-17.9	48	I
1 month into Herceptin	48	47	-15.1	102	II-III
6 weeks	56	60	-19.2	17	I
6 months	53	54	-17.8	8	I
9 months	53	58	-18.1	3	I
12 months	53	55	-17.1	2	I
24 months	52	54	-17.9	-	I

Figure 1: CMR tools to understand the underlying mechanisms of cardiotoxicity. (Panels A and B) Cardiac MRI studies in a patient during and after 6-month withdrawal of trastuzumab: end-diastolic (EDV) frame, end-systolic (ESV) frame, feature tracking analysis and curves and native T1 mapping. At 6-month withdrawal, both EDV and ESV are reduced, ejection fraction increased, longitudinal strain improved, and native T1 values were reduced. This case demonstrated the reversible nature of trastuzumab cardiomyopathy. (Panel C) CMR study in a patient with anthracycline-cardiomyopathy, with reduced EDV and ESV, reduced ejection, impaired global longitudinal strain, and presence of subepicardial and mid-wall late gadolinium enhancement (LGE) in the septum, inferior and inferolateral walls.

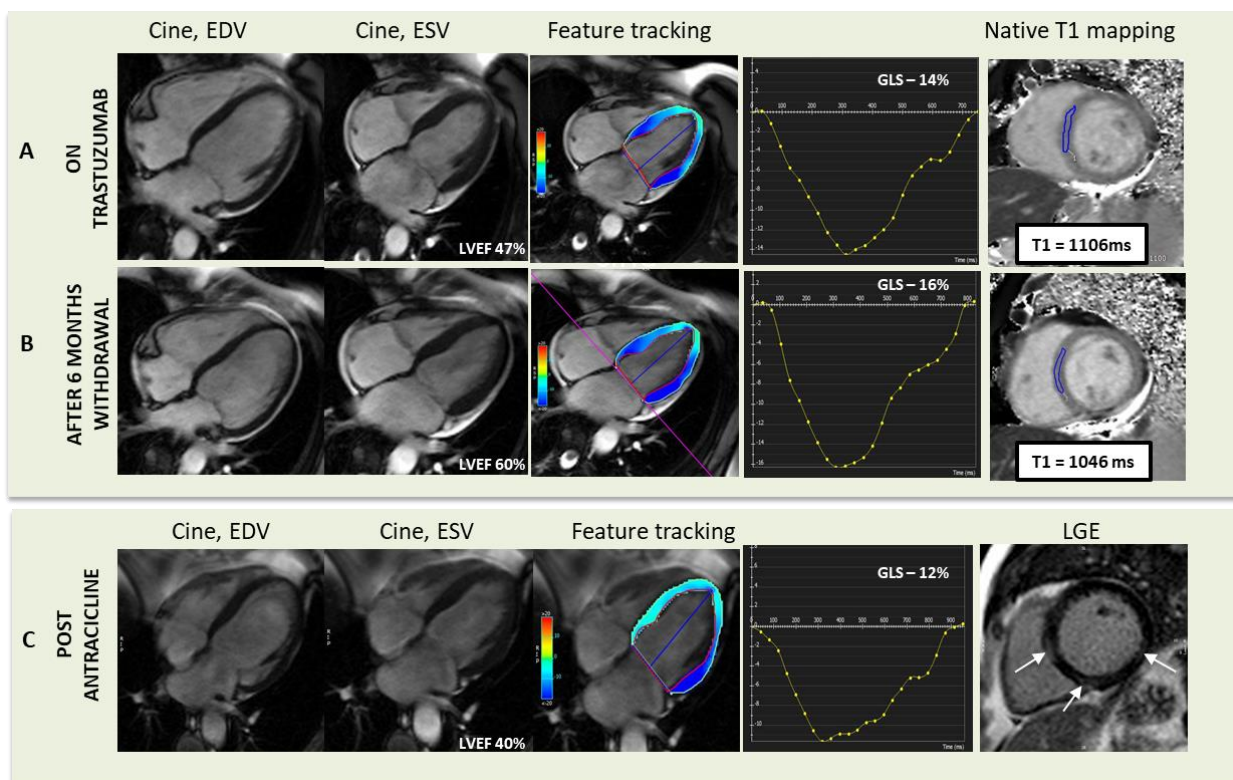


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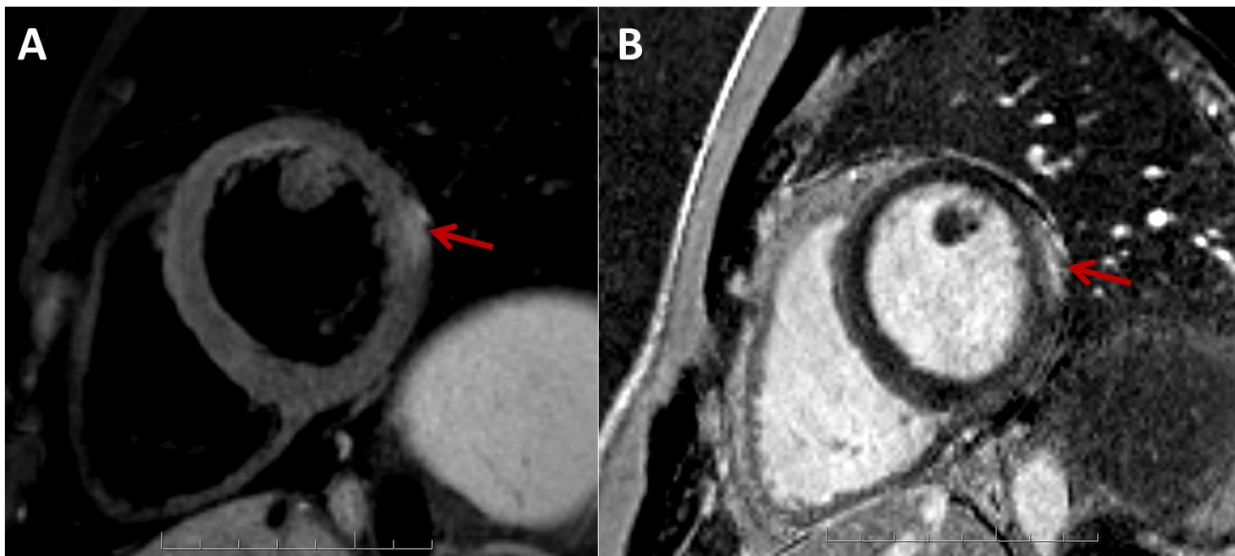


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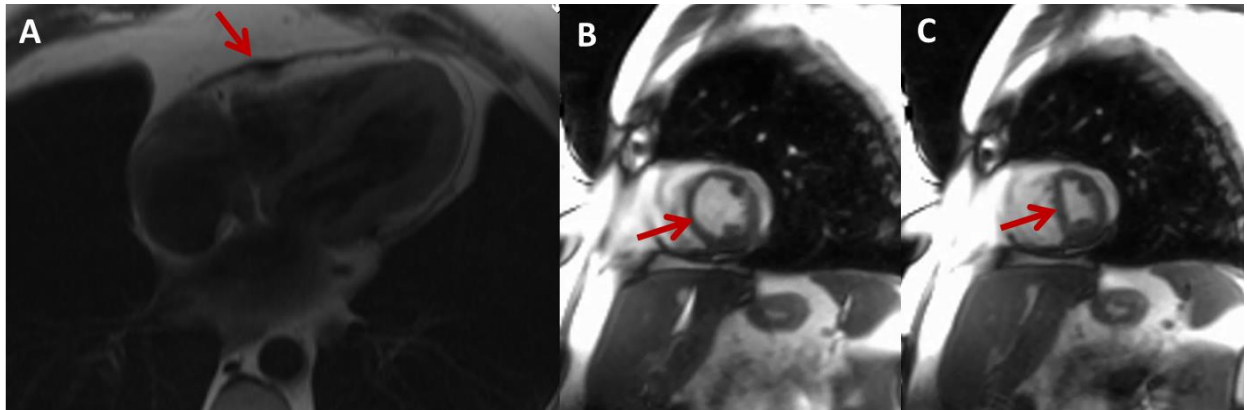


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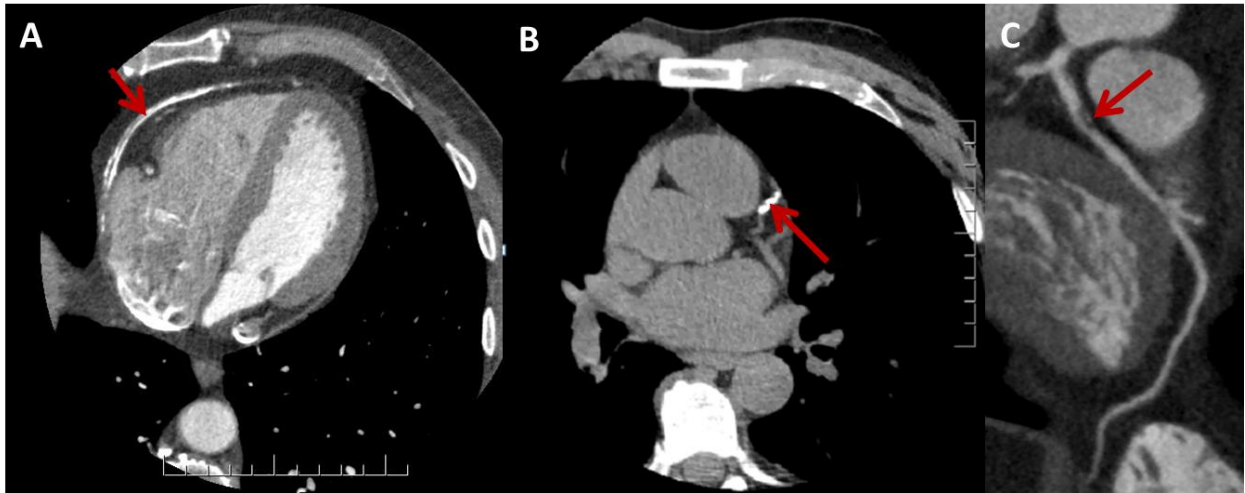


Figure #5: Significant peri-infarct ischemia (panel A, white arrow) in the basal to mid-cavity of the anterior wall (LAD territory) in a 57 year old male with a prior history of chemotherapy and radiation for small cell lung cancer.

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